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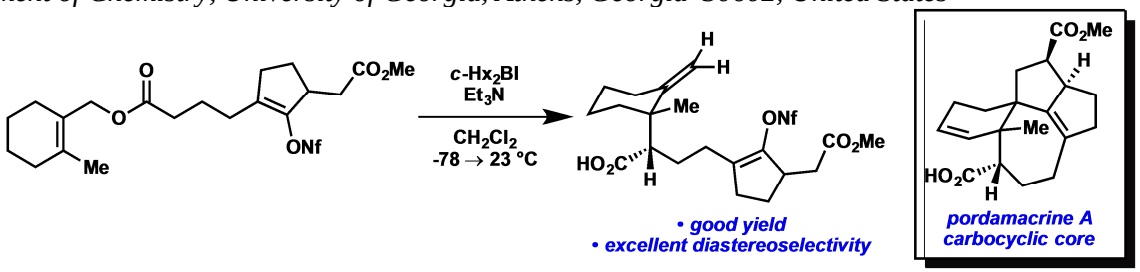

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ABSTRACT

A synthetic approach to pordamacrine A that features two key transformations is discussed. The first transformation applies an Ireland-Claisen rearrangement to establish sterically congested vicinal carbon centers. Although a hard enolization technique for accessing the silyl ketene acetal failed, a soft enolization, boron-based reaction was highly successful. The second step involves a proposed cascade palladium-catalyzed biscyclization to construct two carbocycles of the natural product. The overall strategy is presented, demonstrating the challenges of the cyclization events in this complex setting.

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Introduction

Pordamacrine A (**1**, Fig. 1) is a heavily oxygenated, hexacyclic alkaloid isolated from the leaves of *daphniphyllum macropodum* in 2009.[1] The natural product belongs to a family of over 200 alkaloids produced by the *daphniphyllum* genus.[2] These alkaloids appear to share the common biogenic ancestor squalene, which is elaborated to the complex architecture of these molecules through a polycyclization cascade postulated by Heathcock[3] and supported by a now classic synthesis of methyl homosecodaphniphyllate.[4] Along with other syntheses by Heathcock,[5] members of this family have been the targets of numerous total syntheses and synthetic studies.[6] At least part of the reason for this is that the complex structures of these alkaloids can provide a rich ground for reaction development, owing to the likelihood of encountering difficulties during the course of studies toward a total synthesis.

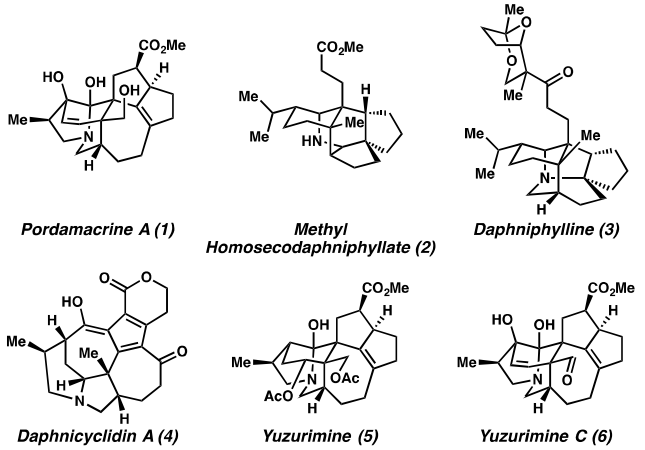


Fig. 1. Representative daphniphylline alkaloids.

This opportunity is certainly true in the case of the yuzurimine subfamily. Although a total synthesis of an alkaloid in this subfamily has yet to be completed, several groups have demonstrated interesting approaches (Fig. 2). Among these efforts have been a pair of strategies by Coldham that employ an intramolecular nitrone dipolar cycloaddition as a key step (eqs 1,2).[6c,d] The group of Bélanger centered their strategy around a tandem intramolecular Vilsmeier-Haack/azomethine ylide cycloaddition sequence (eq 3),[6e] and more recently Hakayawa and Kigoshi took advantage of an intramolecular Wittig reaction to close the yuzurimine central seven-membered ring (eq 4).[6m] Herein, we describe our own synthetic approach toward the yuzurimine alkaloid pordamacrine A, wherein a relatively unexplored variant of the Ireland-Claisen rearrangement enabled us to establish a crucial congested stereodiad within the molecule. This effort is representative of the potential utility of the Ireland-Claisen rearrangment using boron-based enolates, which both our group[7] and the Zemribo group[8] have exploited in recent synthetic and methods studies.

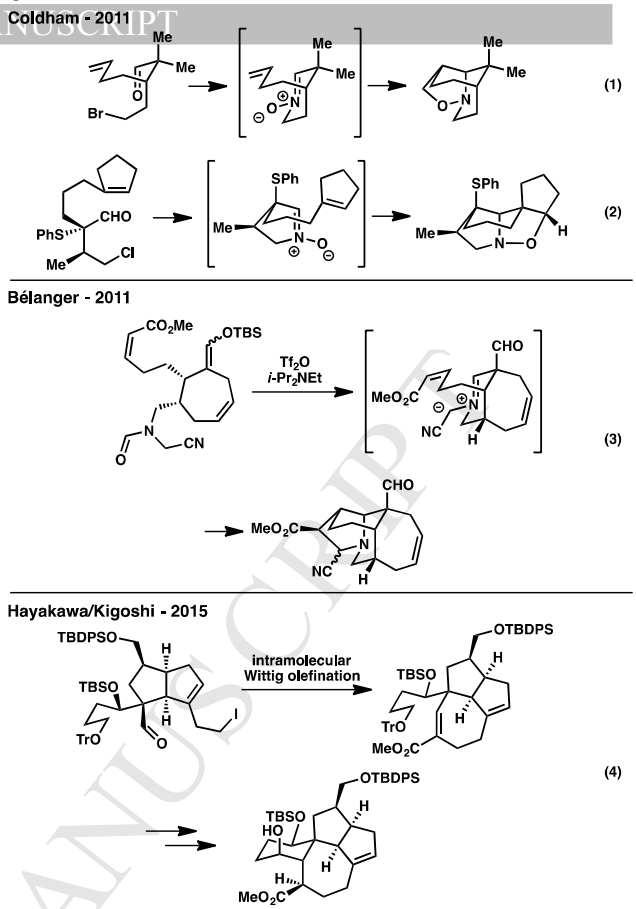


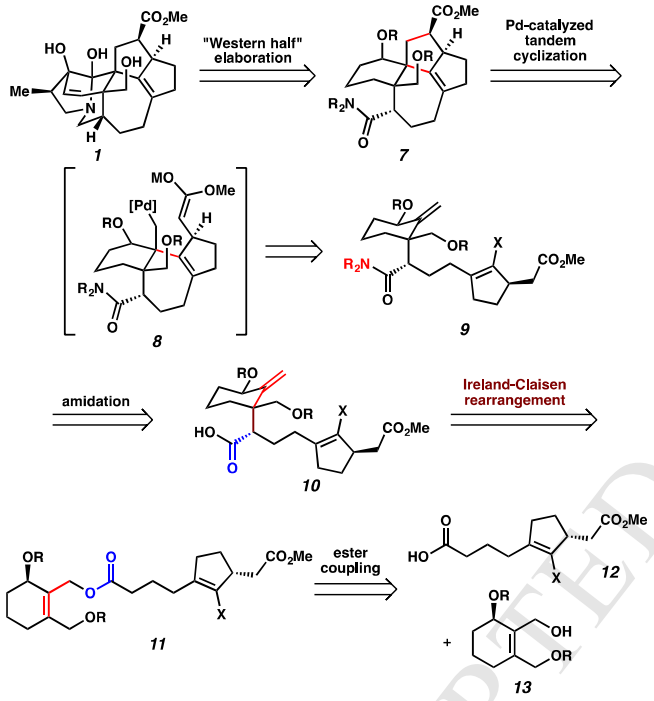
Fig. 2. Previous synthetic approaches to the yuzurimine alkaloids.

Background. Sigmatropic rearrangements occupy a privileged position in the toolbox of synthetic chemists. Their impact is due in part to their ability to enable difficult bond formations with predictable stereoselectivity by rendering them intramolecular. Among these transformations is the Ireland-Claisen rearrangement.[9,10] This reaction facilitates what is formally an ester enolate allylation through the prior formation of an ester linkage between the fragments that will ultimately be connected by a C–C bond. The utility of this transformation is based on the general reliability of methods for both forming the ester precursor and accomplishing the rearrangement itself. Its use in numerous total syntheses, oftentimes as a key step, underscores the notion that the Ireland-Claisen rearrangement is indeed a transformation of fundamental importance.[11]

The classical conditions for effecting the reaction involve first forming a silyl ketene acetal by low temperature hard enolization of an allylic ester by a strong base such as LDA, and *in situ* trapping of the enolate with a silylating agent. The resulting silyl ketene acetal is then heated, either after prior purification or in the same pot to induce the rearrangement itself.[9] This protocol is by far the most commonly utilized method for executing the Ireland-Claisen rearrangement; however, other procedures exist. A limited body of work emerged in the early 1990s demonstrating the viability of phosphorus[12] (by hard enolization) and boron[13] and silicon[14] (by soft enolization) ketene acetals in the Ireland-Claisen rearrangement. Importantly, these methods had not been tested with complex, polyfunctional substrates in the context of total synthesis, until the recent elegant work of Zemribo and coworkers on the successful approaches toward pyrrolidine-based natural products.[8] As described herein, the boron-based strategy proved to be a successful alternative to silicon in the context of our approach toward pordamacrine A.

Results and Discussion

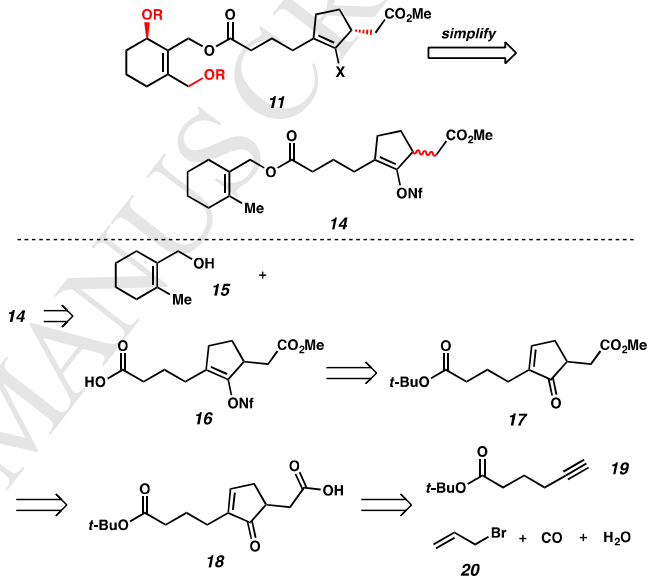
Our retrosynthesis of pordamacrine A (**1**) is outlined in Scheme 1. We planned to delay most of the elaboration of the western half of the molecule until the last stages of the synthesis because we anticipated that the high level of oxygenation present on the cyclohexene ring could cause difficulties with the transformations required to assemble the molecule's carbocyclic skeleton (**7** → **1**). This assembly would revolve around two main steps. The first key step involved a proposed palladium-catalyzed cascade cyclization to establish the cycloheptene and cyclopentane rings of the natural product. Upon oxidative addition of the alkenyl-X species, the closure of the central seven-membered ring would occur by an intramolecular Pd-catalyzed migratory insertion reaction, while the five-membered ring formation would occur by the trapping of the resultant captive neopentyl palladium species **8** by the pendant ester enolate. This proposed process essentially represents a novel enolate-coupling interception of the Heck reaction pathway.



Scheme 1. Proposed retrosynthetic approach to pordamacrine A.

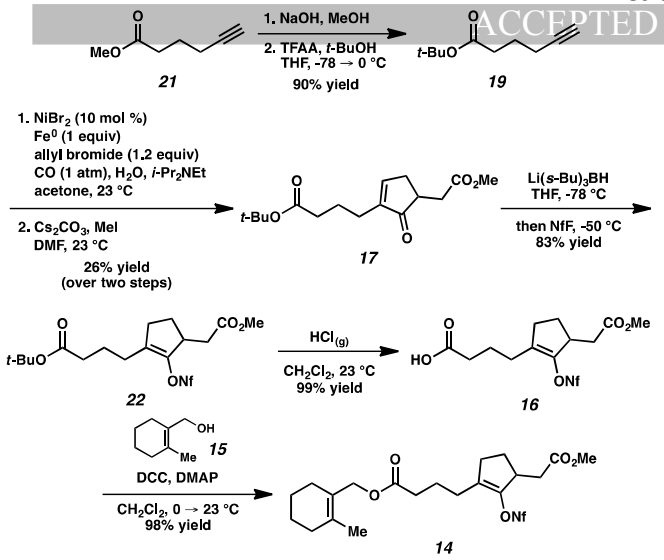
There is an extensive body of literature on the use of the intramolecular Heck reaction to form congested rings;[15] to our knowledge, however, there has been no report of the alkylation of enols/enolates by neopentyl Pd species such as intermediate **8**. The alkylation of vinyl- and aryl-Pd species by enolates, meanwhile, has been extensively explored,[16] suggesting some conceptual feasibility for this approach. The precursor to this proposed cascade, amide **9**, would arise from acid **10**. The synthesis of this acid could be achieved via an Ireland-Claisen rearrangement of allylic ester **11**. We believed this strategy would be highly advantageous for the construction of the congested, stereochemically complex γ,δ-unsaturated acid motif. Finally, allylic ester **11** would be synthesized via standard esterification between acid **12** and alcohol **13**.

We acknowledged the fact that our tandem Pd-catalyzed double cyclization reaction was fairly speculative, and therefore we employed a model system to begin our investigations. We simplified the approach by removing the additional oxygenation on the cyclohexenyl system, reducing our target ester for the Ireland-Claisen rearrangement to compound **14** (Scheme 2). In this compound, we also chose to use an alkenyl sulfonate as the functional group for oxidative addition in the proposed palladium cascade. This group was selected as we envisioned it could readily arise from a carbonyl precursor. Because we anticipated the final steps to allylic ester **14** from *t*-butyl ester **17** would be fairly straightforward, our synthetic route was based around one major consideration – how to prepare the alkenyl sulfonate moiety of acid **16** as a single positional alkene isomer. This requirement ruled out a scheme that involved the enolization and trapping of a saturated ketone, because it was unlikely that kinetic bases would be able to discriminate between the two methine protons adjacent to this ketone. A reduction of cyclopentenone **17** with concomitant trapping of the enolate appeared to be a viable alternative; similar examples indicated promise for this approach.[17] Cyclopentenone **17** would arise from esterification. Finally, we anticipated that cyclopentenone **18** would be expeditiously available via a catalytic, multicomponent cyclocarbonylation reaction as described by Moretó.[18]



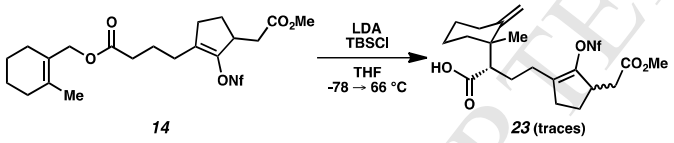
Scheme 2. Model study of proposed cascade transformation - retrosynthetic analysis of substrate **14**.

In the forward sense, we prepared the *t*-butyl ester precursor to the cyclocarbonylation reaction (**19**) by a straightforward, two step transesterification sequence from commercially available methyl hex-5-ynoate (**21**, Scheme 3). The cyclopentenone synthesis gave acceptable yields of diester **17** after alkylation of the acid reaction product with MeI and Cs_2CO_3. Although the yield was modest, the low step count and scalability of the reactions assured that we could produce the necessary amounts of our substrates for the key steps to conduct studies. Reduction of cyclopentenone **17** with Li(*s*-Bu)$_3$BH followed by *in situ* sulfonation of the resultant enolate with NfF cleanly provided alkenyl nonaflate **22**. Here, we opted to use the nonaflate group rather than the more traditional triflate due to the former's known susceptibility to nucleophiles compared to the latter.[19] Such a side reaction could complicate the Pd-catalyzed cyclization step in our planned synthesis. Finally, transesterification of *t*-butyl ester **22** to allylic ester **14** proceeded straightforwardly in near quantitative yield in two steps by HCl-catalyzed *t*-butyl ester cleavage followed by DCC coupling[20] with known allylic alcohol **15**.[21]



Scheme 3. Synthesis of diester **14**.

Having thus secured a route to allylic ester **14**, we turned our attention to the pivotal Ireland-Claisen step (Scheme 4). The C–C bond that would be formed in this step is between two stereogenic centers, one tertiary and the other quaternary. In addition, allylic ester **14** contains a distal ester moiety, capable of both competing enolization and other side reactions. Partially encouraging, this distal ester featured branching at the β position, which should kinetically disfavor enolization to a small extent. The widely demonstrated generality of this rearrangement bolstered our confidence that it would provide us with our desired product, acid **23**. To our chagrin, the standard conditions for effecting the rearrangement *via* a Z-ketene acetal (LDA, HMPA, TBSCl; -78 to 66 °C)[10] led to a complex mixture that contained only traces of the expected acid (**23**). Unfortunately, the intractable mixture of products obtained was unsuitable for the progression of our synthetic studies. It was therefore incumbent upon us to find alternative conditions for the rearrangement step.



Scheme 4. Attempted Ireland-Claisen rearrangement of diester **14** using hard enolization technique.

It was difficult to determine the cause of this failed reaction based on the complex mixture of products that were observed. It seemed likely, however, that the strongly basic conditions used to create the silyl ketene acetal of allylic ester **14** played a role. We therefore turned our attention to conditions that would employ a milder base, i.e., soft enolization conditions. Among the aforementioned systems utilizing soft enolization techniques,[13,14] we were especially intrigued by boron.

Early work from Corey[13a] and Oh[13b] indicated the feasibility of using boron-based enolates in the Ireland-Claisen rearrangement (Fig. 3). In 1991, Corey and Lee described an enantioselective process mediated by a bissulfonamidyl bromoborane (Fig. 3a). Here, the control of the enolate geometry can be achieved with solvent and base selection, and that enolate geometry transfers effectively to the diastereoselection in the rearrangement. The reaction times, however, were protracted, requiring 7 to 14 days to reach completion. Oh and coworkers in 1992 demonstrated a related process using common dialkylboron triflates (Figure 3b). Reaction times were considerably shorter (reported to be less than 5 min at 25 °C), but yields and diastereoselectivities were low for compounds lacking α-alkoxy groups. Subsequent to those reports, boron ketene acetals have been shown to be generated at low temperatures using strong boron electrophiles of the type R_2BI and R_2BOTf in conjunction with a weak base, and can be prepared as either isomer with high geometrical purity.[22] The ability to achieve high geometrical purity offered the potential for high diastereoselectivity in this particular desired transformation. Since the cases outlined in Fig. 2 preceded the reports of efficient methods for the generation of boron enolates from esters, we felt it was necessary to reexamine this variant of the Ireland-Claisen rearrangement with those methods in mind.

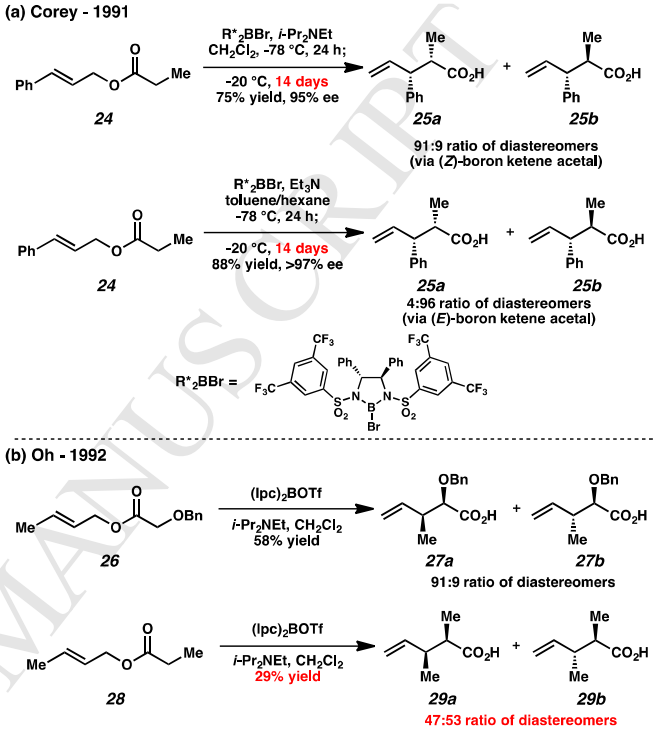
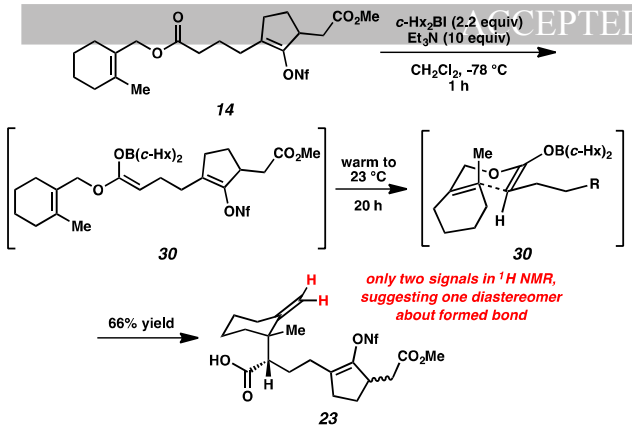


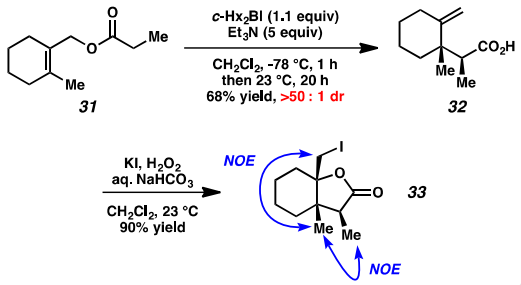
Fig. 3. Early cases of boron-based enolate Ireland-Claisen rearrangements.

The diastereoselectivity of the Ireland-Claisen rearrangement has been thoroughly investigated by Ireland and coworkers.[9,23] On the basis of these studies, we determined that acid **23** would arise via a chairlike transition state from (*Z*)-boron ketene acetal **30** (Scheme 5).[24] Fortunately, highly Z-selective generation of boron ketene acetals of *n*-alkyl esters is possible using *c*-Hx_2BI in conjunction with Et_3N at -78 °C.[22a] To our delight, these conditions (using 2.2 equiv of *c*-Hx_2BI to enolize both esters) followed by warming to room temperature effected smooth rearrangement of allylic ester **14** to acid **23** as apparently a single diastereomer about the formed bond. (The product existed as a mixture of diastereomers epimeric at the distal methyl acetate moiety).



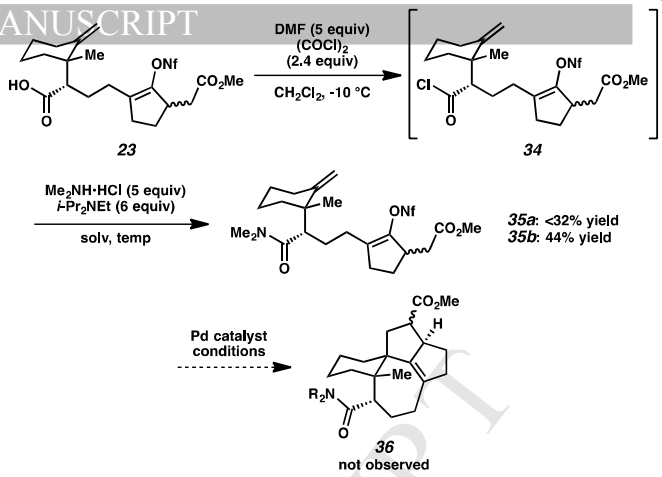
Scheme 5. Boron-mediated Ireland-Claisen rearrangement of diester **14**.

To further study this rearrangement as well as ascertain its diastereoselectivity, we turned our attention to allylic propionate **31** (Scheme 6). On treatment of propionate **31** to the conditions similar to our more complex substrate, except with 1.1 equiv *c*-Hx_2BI/5 equiv Et_3N, we obtained very similar yields. The comparable yield suggests that the polyfunctional nature of diester **14** was well tolerated. To lend support to our stereochemical assignment, we prepared the iodolactone of acid **32**. The proximity of the indicated functional groups in iodolactone **33** was determined by 2D NOE correlations, supporting our stereochemical assignment of **23**.



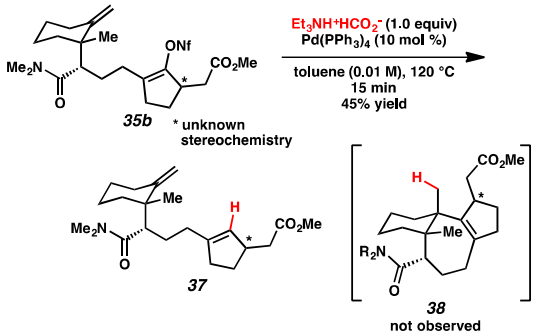
Scheme 6. Analogous stereochemical analysis - rearrangement/iodolactonization of ester **31**.

The acid moiety of rearrangement product **23** would likely render it less suitable as a substrate for our tandem cyclization; we anticipated the basic conditions would lead to a doubly deprotonated species that may lead to unnecessary complications (e.g., solubility profile, etc.). We therefore opted to transform it to an amide, much like what we envisioned would be used in our planned synthesis (Scheme 7). Mild amidation conditions failed to give any detectable product, so we chose to activate acid **23** by forming the acyl chloride (**34**), followed by *in situ* trapping with Me_2NH. The resulting amide existed as mixture of two products (**35a** and **35b**) that we suspected were epimeric at the cyclopentyl stereocenter.[25] Under a variety of conditions expected to effect both the migratory insertion and enolate alkylation steps, we obtained no evidence of seven-membered ring closure, with isolable products always retaining the *exo*-methylene moiety. We frequently observed palladium precipitation from the reaction mixture in these experiments. One can envision a situation where the captive neopentylpalladium species resulting from migratory insertion does not undergo trapping by the pendant enol/enolate nucleophile. This intermediate could simply undergo a β-alkyl elimination process, reversing the ring closure. Without a readily available pathway to terminate the catalytic cycle, the catalyst may simply precipitate from the reaction mixture.



Scheme 7. Amidation and attempted proposed Pd-catalyzed biscyclization.

We reasoned that a reliable method for terminating this catalytic cycle, indeed one that was precedented in the context of ring formation via migratory insertion, could provide insight into this reaction. A reductive Heck cyclization appeared to be an attractive option. To our knowledge, the formation of a seven-membered ring terminated by alkylpalladium reduction in this reaction manifold is unknown, but analogous five- and six-membered ring formations from alkenyl halides have been described.[26] Under dilute conditions we treated amide **35b** with triethylammonium formate in the presence catalytic $Pd(PPh_3)_4$ (Scheme 8). Instead of cyclization, this reaction led only to simple reduction of the alkenyl sulfonate moiety. It appears, therefore, that formation of this seven-membered ring is disfavored. Close examination of molecular models suggests a reason for this lack of reactivity. For the seven-membered ring to close, the alkenylpalladium species resulting from oxidative addition and the *exo*-methylene group need to come into close proximity. This forces the molecule to adopt a conformation that places the dimethylamide moiety directly underneath the six-membered ring, thereby creating severe non-bonded interactions that may disfavor this reactive conformation. Based on this conformational analysis, it seemed a fundamental feature of this substrate created problems that even judicious choice of catalytic conditions would be unlikely to solve.[27]



Scheme 8. Pd-catalyzed reduction of nonaflate **35b**.

Conclusion

We have described herein our studies toward the total synthesis of pordamacrine A, featuring a successful execution of the boron-based Ireland-Claisen rearrangement in a complex system. Although the proposed cascade cyclization was unsuccessful on the model system we investigated, important insights were obtained about the structural limitations of the synthetic approach. Regardless, this approach demonstrated the potential utility of the boron-based Ireland-Claisen

rearrangement, as we were able to successfully employ this method in this structurally complex setting. The diastereoselectivity of the specific transformation was excellent, predicated on the highly organized transition state by which this process occurs. We believe that this example illustrates the capacity of this rearrangement to establish complex stereochemical arrays, and we anticipate that this method will thus be of high use for the synthetic community. Further efforts in related synthetic areas are underway.

Experimental Section

Materials and Methods. Reactions were performed under an argon atmosphere unless otherwise noted. Dichloromethane, tetrahydrofuran, *N*,*N*-dimethylformamide, and toluene were purified by passing through activated alumina columns. Triethylamine and diisopropylethylamine were distilled under Ar from CaH_2. Nonafluorobutanesulfonyl fluoride was purchased from Synquest Laboratories (Alachua, FL) and purified according to Lyapkalo and coworkers.[28] All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), or Strem Chemicals (Newport, MA). Visualization was accomplished with UV light and exposure to $KMnO_4$ solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^{1}H NMR spectra were acquired on a Varian 400 MR (at 400 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 101 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.0). ^{19}F NMR spectra were acquired on a Varian 400 MR (at 376 MHz) and are reported in ppm relative to HF (δ 0.0). Infrared spectra were recorded as films on a Nicolet iS-50 FTIR. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS; low resolution mass spectrometry data were acquired on an Agilent 6100 Single Quad LC/MS.

Notes on handling *c*-Hx$_2$BI. Dicyclohexyliodoborane is a very water and oxygen sensitive compound that must at all times be handled and stored under an inert atmosphere. The pure reagent is a clear, colorless liquid at room temperature. Material kept in septum-capped bottles, either neat or in solution, discolors on the order of days to weeks, and strongly colored reagent gives inferior results. After careful experimentation, we found the following protocol to be useful: after synthesis of the reagent by the method of Brown,[22a] the crude material was distilled into a Schlenk flask. On completion of the distillation, the product-containing flask was stoppered under an Ar purge and immediately evacuated. The flask was taken into an N_2 atmosphere glove-box, transferred to a brown glass bottle, and stored at room temperature. Material stored in this way showed no evidence of decomposition after several months had elapsed. The reagent was removed from the glove-box in a syringe as needed and added to a reaction mixture or diluted with hexanes to make a stock solution that was used immediately.

Ester 19 (*tert*-butyl hex-5-ynoate). To a solution of methyl ester **21** (methyl hex-5-ynoate, 15.5 g, 123 mmol) in MeOH (160 mL) and H_2O (40 mL) at ambient temperature was added KOH pellets (85%, 15.5 g, 184 mmol). The solution was stirred for 30 min, at which point TLC indicated consumption of the starting material. The solution was quenched with sat. aq. NH_4Cl, and the MeOH was removed by rotary evaporation. The resulting biphasic mixture was diluted with 10% aq. HCl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$, and concentrated in vacuo to afford the carboxylic acid, which was used directly without further purification.

To a solution of the carboxylic acid (assume 123 mmol) in THF (40 mL) at -78 °C was added TFAA (34.1 mL, 245 mmol) over 2 min. The solution was then allowed to warm to ambient temperature. Once it had reached ambient temperature, the solution was recooled to -78 °C, and a solution of *t*-BuOH (18.2 g, 245 mmol) in THF (10 mL) was added. The reaction mixture was then sealed and stirred at 0 °C for 14 h. The reaction mixture was then poured into a stirring solution of K_2CO_3 (50.9 g, 368 mmol) in H_2O (200 mL) at a rate such that evolution of CO_2 was controlled. The resulting mixture was then extracted with pentane (3 x 50 mL), and the combined organic extracts were washed with H_2O (2 x 200 mL), then dried with $MgSO_4$ and applied directly to a SiO_2 column (3 x 15 cm), eluting with 9:1 pentane/Et_2O. The combined product-containing fractions were concentrated to give ester **19** (18.6 g, 90% yield over 2 steps) as a colorless liquid.

Data for ester **19**. TLC: R_f = 0.36 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (t, *J* = 7.4 Hz, 2H), 2.23 (td, *J* = 6.9, 2.5 Hz, 2H), 1.94 (t, *J* = 2.5 Hz, 1H), 1.79 (app. quintet, *J* = 7.2 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.4, 83.5, 80.3, 68.8, 34.2, 28.1, 23.8, 17.8. IR (film): ν = 3296, 3005, 2975, 2935, 2119, 1723, 1367, 1144 cm^{-1}. HRMS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{10}H_{16}O_2 + NH_4]^+$: 186.1489, found 186.1493.

Cyclopentenone 17 (*tert*-butyl 4-(4-(2-methoxy-2-oxoethyl)-5-oxocyclopent-1-en-1-yl)butanoate). In a 250 mL round bottom flask charged with a large stirbar, a mixture of $NiBr_2$ (1.09 g, 5.00 mmol), NaI (3.00 g, 20.0 mmol), and Fe powder (10 μm particle size, 2.79 g, 50.0 mmol) was stirred under vacuum for 10 min at room temperature. The flask was then backfilled with CO, fitted with a CO balloon, and charged with acetone (25 mL). The resulting suspension was stirred for 30 min, during which the color changed from dark red to pale green. A portion of water (1.00 mL, 55.5 mmol) was added at the end of this period. Next, a solution of alkyne **19** (8.41 g, 50.0 mmol), allyl bromide (5.19 mL, 60.0 mmol), and *i*-Pr_2NEt (0.218 mL, 1.25 mmol) in acetone (10 mL) was added via syringe pump at a rate of 8.0 mL/h. The stirring during the addition was extremely vigorous to keep the solution saturated with CO. At the end of the addition, the reaction mixture was stirred for an additional 1 h at room temperature. The solvent was then removed in vacuo. The resulting residue was dissolved in CH_2Cl_2 (50 mL), and filtered through a plug of celite, rinsing with CH_2Cl_2. The filtrate was washed sequentially with 10% aq. HCl (3 x 50 mL), H_2O (50 mL), and brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting crude product was used in the next step without further purification.

The crude product was dissolved in DMF (50 mL) at 23 °C, and treated sequentially with dry Cs_2CO_3 (9.77 g, 30.0 mmol) and MeI (6.24 mL, 100 mmol). The resulting solution was stirred 14 h at ambient temperature then poured into H_2O (100 mL) and extracted with pentane (3 x 50 mL). The pentane extracts were washed with 10% aq. LiCl (50 mL), followed by brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to give diester **17** (3.79 g, 26% yield) as a colorless liquid.

Data for diester **17**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (br. s, 1H), 3.66 (s, 3H), 2.86 (ddd, *J* = 18.8, 6.7, 3.1 Hz, 1H), 2.82 (dd, *J* = 16.5, 4.1 Hz, 1H), 2.68 (dddd, *J* = 9.3, 6.7, 4.1, 2.7 Hz, 1H), 2.40 (dd, *J* = 16.5, 9.3 Hz, 1H), 2.29 (app. dt, *J* = 18.8, 2.3

Hz, 1H), 2.21 (t, *J* = 7.4 Hz, 2H), 2.22-2.16 (comp. m, 2H), 1.76 (app. quintet, *J* = 7.4 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.2, 172.6, 172.4, 156.2, 144.7, 80.2, 51.7, 41.6, 35.0, 34.9, 33.6, 28.1, 24.3, 23.0.

Alkenyl nonaflate 22 (*tert*-butyl 4-(3-(2-methoxy-2-oxoethyl)-2-(((perfluorobutyl)sulfonyl)oxy)cyclopent-1-en-1-yl)butanoate). To a solution of cyclopentenone **17** (3.79 g, 12.8 mmol) in THF (20 mL) at -78 °C was added Li(*s*-Bu)$_3$BH (13.4 mL, 1.0 M in THF, 13.4 mmol) over 5 min. The resulting solution was stirred 10 min then treated with NfF (2.98 mL, 16.6 mmol). The resulting biphasic mixture was stirred 60 s, then removed from the dry ice/acetone bath and allowed to warm 5 min before placing in a -20 °C bath. The reaction mixture became homogeneous in 5 min, and an additional portion of NfF was added (0.460 mL, 2.56 mmol). The reaction mixture was stirred an additional 30 min, and then quenched with H_2O (1.0 mL). The resulting solution was cooled to -78 °C and treated slowly (caution: exothermic!) with H_2O_2 (30% in H_2O, 5.50 mL, 51.2 mmol). The dry ice bath was removed, and the solution heated under its own exotherm to ~40 °C. The quenched reaction mixture was poured into H_2O (150 mL) and 1 M aq. NaOH (50 mL), and the resulting mixture was extracted with pentane (3 x 50 mL). The combined organic extracts were washed sequentially with H_2O (100 mL), 1 M aq. NaOH (50 mL), and brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to give alkenyl nonaflate **22** (6.19 g, 83% yield) as a colorless liquid.

Data for alkenyl nonaflate **22**. TLC: R_f = 0.09 (9:1 hexanes/EtOAc, $KMnO_4$ stain solution). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H), 3.31 (br. s, 1H), 2.65 (dd, *J* = 15.7, 3.9 Hz, 1H), 2.44-2.09 (comp. m, 8 H), 1.80-1.57 (comp. m, 3H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 171.9, 143.6, 134.0, 80.4, 51.7, 40.0, 37.1, 34.9, 28.9, 28.0, 26.4, 26.1, 22.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -80.7 (t, *J* = 9.5 Hz, 3F), -110.3 (tq, *J* = 15.0, 2.7 Hz, 2F), -120.9 (m, 2F), -125.9 (m, 2F). IR (film): ν = 2978, 2955, 2855, 1729, 1238, 1199, 1143, 909 cm^{-1}. HRMS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{20}H_{25}F_9O_7S + NH_4]^+$: 598.1516, found 598.1540.

Carboxylic acid 16 (4-(3-(2-methoxy-2-oxoethyl)-2-(((perfluorobutyl)sulfonyl)oxy)cyclopent-1-en-1-yl)butanoic acid). An apparatus to generate HCl gas was assembled by charging a 50 mL Schlenk flask with ~50 g NaCl. The flask was capped with a rubber septum and the side arm fitted with PVC tubing connected to a long 18 gauge needle. The needle was immersed in a solution of ester **22** (5.00 g, 9.11 mmol) in CH_2Cl_2 (91 mL) at ambient temperature in a 250 mL round bottom flask fitted with a rubber septum and an outlet needle. The solution was sparged with HCl gas by slowly adding H_2SO_4 (98%, 6.0 mL) to the Schlenk flask containing NaCl at a rate so as to control the evolution of gas. Near the end of the addition, the HCl gas needle was raised above the level of the solution and the outlet needle was removed to create a slight positive pressure of HCl in the flask. When the addition was complete, the needle was removed altogether, and the flask was sealed with parafilm and stirred 16 h at ambient temperature. At the end of this time, TLC indicated consumption of the starting material. The reaction mixture was then poured into H_2O (50 mL), the organic phase separated, and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to afford acid **16** (4.45 g, 99% yield) as a pale brown liquid.

Data for acid **16**. TLC: R_f = 0.01 (9:1 hexanes/EtOAc, $KMnO_4$ stain solution). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.25 (br. s, 1H), 3.67 (s, 3H), 3.34-3.24 (m, 1H), 2.64 (dd, *J* = 15.7, 3.9 Hz, 1H), 2.39-2.14 (comp. m, 8H), 1.83-1.63 (comp. m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.8, 171.9, 143.8, 133.5, 51.7, 40.0, 36.9, 33.2, 28.9, 26.4, 26.0, 21.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -80.7 (t, *J* = 9.5 Hz, 3F), -110.2 (tq, *J* = 15.0, 2.7 Hz, 2F), -120.9 (m, 2F), -125.9 (m, 2F). IR (film): ν = 3000 (br), 2957, 1739, 1711, 1419, 1235, 1197, 1141, 1033 cm^{-1}. HRMS (ESI): *m/z* calc'd for $(M + Na)^+$ $[C_{16}H_{17}F_9O_7S + Na]^+$: 547.0443, found 547.0446.

Ester 14 ((2-methylcyclohex-1-en-1-yl)methyl 4-(3-(2-methoxy-2-oxoethyl)-2-(((perfluorobutyl)sulfonyl)oxy)cyclopent-1-en-1-yl)butanoate). To a solution of (2-methylcyclohex-1-en-1yl)methanol[21] (**15**, 1.21 g, 9.55 mmol), acid **16** (5.15 g, 9.09 mmol), and DMAP (56.0 mg, 0.455 mmol) in CH_2Cl_2 (9.1 mL) at 0 °C was added DCC (2.06 g, 10.0 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring for an additional 12 h. At this point, TLC indicated that acid **16** remained, so additional charges of alcohol **15** (126 mg, 0.909 mmol) and DCC (206 mg, 1.00 mmol) were added. The reaction mixture was stirred an additional 12 h, until TLC showed consumption of acid **16**. The reaction mixture was then diluted with hexanes (20 mL) and filtered (through plug? frit?), rinsing with hexanes (20 mL). The filtrate was concentrated, and the crude product was further purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to give ester **14** (6.02 g, 98% yield) as a pale yellow liquid.

Data for ester **14**. TLC: R_f = 0.27 (9:1 hexanes/EtOAc, $KMnO_4$ stain solution). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (s, 2H), 3.66 (s, 3H), 3.34-3.22 (m, 1H), 2.63 (dd, *J* = 15.7, 3.9 Hz, 1H), 2.38-2.11 (comp. m, 8H), 2.02-1.92 (comp. m, 4H), 1.82-1.63 (comp. m, 3H), 1.67 (s, 3H), 1.66-1.50 (comp. m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.2, 171.9, 143.7, 133.8, 133.6, 125.0, 64.9, 51.7, 40.0, 37.0, 33.7, 31.9, 28.9, 27.7, 26.4, 26.1, 22.78, 22.75, 22.1, 19.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -80.7 (t, *J* = 10.2 Hz, 3F), -110.3 (t, *J* = 15.0 Hz, 2F), -120.9 (m, 2F), -125.9 (m, 2F). IR (film): ν = 2933, 2859, 1737, 1419, 1235, 1198, 1142, 1033, 852 cm^{-1}. HRMS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{24}H_{29}F_9O_7S + NH_4]^+$: 650.1829, found 650.1823.

Acid 23 (4-(3-(2-methoxy-2-oxoethyl)-2-(((perfluorobutyl)sulfonyl)oxy)cyclopent-1-en-1-yl)-2-(1-methyl-2-methylenecyclohexyl)butanoic acid). A stirred solution of ester **14** (876 mg, 1.39 mmol) and Et_3N (1.94 mL, 13.9 mmol) in CH_2Cl_2 (14 mL) was cooled to -78 °C. Neat *c*-Hx_2BI (0.698 mL, 3.04 mmol) was added dropwise to the reaction mixture at -78 °C, and the resulting mixutre was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 20 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M aq. Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3 x 10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated in vacuo. The resulting residue was dissolved in MeOH (14 mL) and treated with H_2O_2 (1.39 mL, 30% in H_2O, 13.9 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was analyzed by ^{1}H NMR (d1

= 10 s) to obtain a dr of the reaction and then purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **23** (581 mg, 66% yield) as a clear, colorless liquid. (For the ^{1}H NMR spectrum, excepting the signals at 1.08 and 1.10 ppm, the remaining signals of the two diastereomers either appeared as coalesced signals or complex multiplets.)

Data for acid **23**. TLC: R_f = 0.24 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.72 (s, 1H), 4.62 (s, 1H), 3.68 (s, 3H), 3.40-3.22 (m, 1H), 2.92-2.81 (m, 1H), 2.75-2.61 (comp. m, 2H), 2.50-2.01 (comp. m, 7H), 1.89-1.63 (comp. m, 4H), 1.62-1.42 (comp. m, 3H), 1.34-1.13 (comp. m, 3H), 1.10 (s, 1.5H), 1.08 (s, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.9, 178.8, 172.1, 171.9, 153.6, 153.5, 143.9, 143.4, 134.1, 133.6, 108.4, 108.3, 51.8, 51.7, 49.0, 48.6, 44.6, 41.7, 41.6, 40.1, 40.0, 37.12, 37.05, 37.0, 32.8, 29.24, 29.18, 28.0, 27.9, 26.6, 26.5, 26.2, 25.7, 24.1, 23.9, 21.73, 21.70, 21.6, 21.5, 20.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -80.7 (m, 3F), -110.2 (m, 2F), -120.9 (m, 2F), -125.9 (m, 2F). IR (film): ν = 3000 br, 2937, 2859, 1736, 1704, 1421, 1238, 1200, 1144, 907 cm^{-1}. MS (ESI): *m/z* calc'd for $(M + H)^+$ $[C_{24}H_{29}F_9O_7S + H]^+$: 633.2, found 633.2.

Amides 35a/35b (methyl 2-(3-(4-(dimethylamino)-3-(1-methyl-2-methylenecylcohexyl)-4-oxobutyl)-2-(((perfluorobutyl)sulfonyl)oxy)cyclopent-2-en-1-yl)acetate. To a solution of acid **23** (2.20 mg, 3.26 mmol) in CH_2Cl_2 (13 mL) was added DMF (1.26 mL, 16.3 mmol), followed by $(COCl)_2$ (0.651 mL, 7.69 mmol). Toward the end of this addition, a colorless crystalline precipitate formed. The reaction mixture was stirred 5 min at -10 °C, then Me_2NH•HCl (1.33 g, 16.3 mmol) was added in one portion, followed by *i*-Pr_2NEt (3.41 mL, 19.6 mmol) over 30 s. The solution became clear yellow, and it was stirred 30 min at -10 °C before being allowed to warm to ambient temperature. The reaction mixture was then diluted with hexanes (50 mL) and Et_2O (50 mL). The resulting solution was washed sequentially with 1 M aq. HCl (50 mL), H_2O (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (4:1 hexanes/EtOAc → 2:1 hexanes/EtOAc eluent) to give amides **35a** (739 mg, <32% yield) and **35b** (1.00 g, 44% yield), both as pale yellow liquids. Amide **35a** was contaminated with an unidentified impurity that could not be removed.

Data for amide **35a**. TLC: R_f = 0.14 (4:1 hexanes/EtOAc, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (s, 1H), 4.62 (d, *J* = 1.2 Hz, 1H), 3.68 (s, 3H), 3.36-3.24 (m, 1H), 3.11 (dd, *J* = 11.0, 2.4 Hz, 1H), 3.03 (s, 3H), 2.90 (s, 3H), 2.65 (dd, *J* = 15.7, 3.9 Hz, 1H), 2.50-1.22 (comp. m, 17H), 1.14 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -80.6 (m, 3F), -110.3 (m, 2F), -120.9 (m, 2F), -125.9 (m, 2F). IR (film): ν = 2938, 2861, 1737, 1666, 1635, 1418, 1236, 1199, 1143, 1121, 1009 cm^{-1}. HRMS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{34}NO_6F_9S + H]^+$: 660.2036, found 660.2039.

Data for amide **35b**. TLC: R_f = 0.07 (4:1 hexanes/EtOAc, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (s, 1H), 4.64 (s, 1H), 3.68 (s, 3H), 3.36-3.18 (m, 1H), 3.17 (dd, *J* = 11.2, 2.5 Hz, 1H), 3.07 (s, 3H), 2.90 (s, 3H), 2.63 (dd, *J* = 15.7, 3.9 Hz, 1H), 2.46-2.17 (comp. m, 6H), 2.16-2.05 (m, 1H), 2.03-1.83 (comp. m, 2H), 1.78-1.36 (comp. m, 8H), 1.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.2, 153.1, 142.8, 134.8, 108.3, 51.7, 44.4, 42.2, 39.9, 38.2, 37.1, 36.0, 35.6, 33.6, 28.8, 27.8, 26.6, 25.9, 25.8, 23.1, 21.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -80.6 (m, 3F), -110.3 (m, 2F), -120.9 (m, 2F), -125.8 (m, 2F). IR (film): ν = 2933, 2859, 1739, 1418, 1236, 1198, 1142, 1032, 1010 cm^{-1}. HRMS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{34}NO_6F_9S + H]^+$: 660.2036, found 660.2040.

Alkene 37 (methyl 2-(3-(4-(dimethylamino)-3-(1-methyl-2-methylenecyclohexyl)-4-oxobutyl)cyclopent-2-en-1-yl)acetate. A solution of alkenyl nonaflate **35b** (33.6 mg, 0.0509 mmol) in toluene (5.1 mL) was sparged with Ar for 15 min. This solution was transferred to an Ar flushed vial charged with a stirbar and $Pd(PPh_3)_4$ (5.9 mg, 0.00509 mmol). To this solution was added $HCO_2^-Et_3NH^+$ (7.6 mg, 0.0509 mmol), and the solution was immediately heated to 120 °C in a preheated oil bath. The reaction mixture was stirred for 15 min at this temperature and then allowed to cool to ambient temperature. The solution was then passed through a short pad of SiO_2, rinsing with Et_2O (10 mL). The filtrate was concentrated in vacuo and purified by flash column chromatography (9:1 hexanes/EtOAc → 2:1 hexanes/EtOAc) to give pure alkene **37** (8.5 mg, 45% yield) as a pale yellow liquid.

Data for alkene **37**. TLC: R_f = 0.33 (2:1 hexanes/EtOAc, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.29 (br. s, 1H), 4.71 (s, 1H), 4.63 (s, 1H), 3.67 (s, 3H), 3.17-2.98 (m, 1H), 3.13 (app. d, *J* = 8.6 Hz, 1H), 3.04 (s, 3H), 2.90 (s, 3H), 2.39-2.08 (comp. m, 7H), 2.04-1.85 (comp. m, 3H), 1.80-1.71 (m, 1H), 1.70-1.33 (comp. m, 7H), 1.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.7, 173.4, 153.5, 145.4, 127.0, 108.2, 51.4, 43.4, 42.2, 42.0, 40.4, 38.3, 36.1, 35.6, 34.3, 33.7, 30.3, 29.7, 27.8, 26.3, 23.2, 21.9. IR (film): ν = 2929, 1736, 1634, 1438, 1394, 1254, 1165, 1132 cm^{-1}. MS (ESI): *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{35}NO_3 + H]^+$: 362.2690, found 362.2682.

Acid 32 (2-(1-methyl-2-methylenecyclohexyl)propanoic acid). A stirred solution of (2-methylcyclohex-1-en-1-yl)methyl propionate[7] (**31**, 187 mg, 1.03 mmol) and Et_3N (0.710 mL, 5.13 mmol) in CH_2Cl_2 (10.3 mL) was cooled to -78 °C. Neat *c*-Hx_2BI (0.260 mL, 1.13 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 20 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M aq. Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3 x 10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (10 mL) and treated with H_2O_2 (1.03 mL, 30% in H_2O, 10 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,2-dichloroethane was added (20.2 □L, 0.256 mmol) and analyzed by ^{1}H NMR (d1 = 10 s) to obtain a crude yield and dr of the reaction. The chloroform solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **32** (127 mg, 68% yield) as a waxy, colorless solid.

Data for acid **32**. TLC: R_f = 0.32 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (s, 1H), 4.63 (s, 1H), 3.02 (q, *J* = 7.0 Hz, 1H), 2.39 (td, *J* = 14.1, 3.9 Hz, 1H), 2.17 (dt, *J* = 14.1, 2.4 Hz, 1H), 1.77 (app. d, *J* = 13.7 Hz, 2H), 1.55-1.40 (comp. m, 2H), 1.37-1.22 (m, 1H), 1.20-1.11 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.5, 153.8, 108.2,

42.3, 41.3, 37.0, 32.8, 28.1, 21.6, 21.1, 11.2. IR (film): ν = 2967, 2943, 2916, 1733, 1213, 1155, 1027, 963 cm^{-1}. HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{18}O_2 + H]^+$: 183.1380, found 183.1385.

Lactone 33 (7a-(iodomethyl)-3,3a-dimethylhexahydrobenzofuran-2(3H)-one). To a solution of acid **32** (57.9 mg, 0.318 mmol) and KI (106 mg, 0.636 mmol) in a biphasic mixture of 5% aq. $NaHCO_3$ (1.00 mL) and CH_2Cl_2 (1.00 mL) at ambient temperature under air was added H_2O_2 (63.6 □L, 30 % in H_2O, 0.636 mmol) dropwise. The solution was stirred for 5 min at ambient temperature, at which time TLC indicated consumption of the acid starting material. The reaction was then partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was separated and washed with brine (10 mL), dried with Na_2SO_4 and concentrated to afford lactone **33** (88.4 mg, 90% yield) as a colorless, crystalline solid, which did not require further purification. The stereochemistry of lactone **33** was assigned on the basis of NOE data.

Data for lactone **33**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (d, *J* = 11.2 Hz, 1H), 3.44 (d, *J* = 11.2 Hz, 1H), 3.01 (q, *J* = 7.2 Hz, 1H), 2.52 (br. d, *J* = 14.1 Hz, 1H), 1.76-1.08 (comp. m, 7H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 83.5, 44.3, 42.0, 34.6, 32.2, 22.4, 21.0, 19.4, 9.2, 8.7. IR (film): ν = 3357 (br), 2952, 2923, 2854, 1760, 1175, 1118, 1049, 1023, 974, 931 cm^{-1}.

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